

Assessment of Quality of Life of Hepatitis C Virus Patients after Treatment with Direct-Acting Antiviral Drugs

Hani A. El sayed^{1*}, Khalil A. Khalil², Ashraf M. El-Tantawy³,
Nashaat M. Soliman⁴.

¹Department of Internal Medicine, Faculty of Medicine, Mansoura University, Egypt.

²Department of Internal Medicine, Faculty of Medicine-Suez Canal University, Egypt.

³Department of Psychiatry, Faculty of Medicine, Suez Canal University, Egypt.

⁴Department of Endemic and Infectious Diseases, Faculty of Medicine, Suez Canal University, Egypt.

Abstract

Background: Infection with the hepatitis C virus (HCV) is one of the major causes of liver disease around the world. There is some disagreement as to the prognosis of patients with chronic hepatitis C. Most patients with chronic hepatitis C will have a normal life span and not suffer the consequences of this disease. Health-Related Quality of Life (HRQoL) has gained prominence as a tool to assess the impact of chronic diseases and their treatments on the perception of health and patient well-being. **Aim:** To improve health-related quality of life among Egyptian hepatitis C virus patients. **Patients and Methods:** A cross-sectional study was conducted on 80 patients who received direct-acting antiviral agents at the Center of Treatment of Viral Hepatitis in Ismailia Fever Hospital. The statistical analyses were performed according to onset age, the presence of family history, clinical examination, and severity of the disease. **Results:** This study showed the mean score of questionnaires as regards abdominal symptoms were 2.72 in studied patients, fatigue was 3.04, systemic symptoms were 3.20, activity was 3.5, emotional functions were 3.59 and worry was 3.90. **Conclusion:** patients with chronic hepatitis C with or without cirrhosis have markedly reduced HRQOL. Patients who had a sustained response (virological or biochemical) to interferon therapy experienced significant improvements in perceived wellness and functional status. Successful interferon therapy provides meaningful improvements in HRQOL in patients with chronic hepatitis C.

Keywords: Hepatocellular Carcinoma, Chronic Liver Disease.

Introduction

HCV is a blood-borne illness that affects approximately 160 million people worldwide⁽¹⁾, and 2.5% of adults. The incidence is higher in underdeveloped or developing regions, reaching about 4 to 6% in some African communities and the Middle East⁽²⁾. Historically, the infection has been transmitted primarily through blood transfusions and needle-sharing among injection

drug users, though other risk factors have been identified. Screening of donated blood has greatly reduced the rate of new infections worldwide. Since HCV is typically asymptomatic, most new cases go undetected and approximately 75% become chronic⁽³⁾. Chronic HCV infection greatly increases the risk of cirrhosis, liver failure, and hepatocellular carcinoma (HCC). The health consequences of HCV, including cirrhosis and HCC, are more likely as the

*Corresponding Author: hanyahmed1012@gmail.com

length of infection increases. The burden of HCV infection is not limited to the impact of cirrhosis and HCC. Previous research has found that HCV infection is associated with reduced HRQoL, even in the absence of cirrhosis⁽⁴⁾. The evolution of HCV treatment has been swift, dazzling, and unprecedented. In only five years, proof of concept for oral, interferon-free treatment has been established, nine direct-acting antivirals (DAAs) have been approved, treatment duration has been shortened to 12 weeks, and cure rates have been nearly 100% in clinical trials⁽⁵⁾. HRQOL refers to the subjective assessment of patients regarding the physical, mental and social dimensions of well-being. It has become an important measure in clinical and epidemiological studies in gastroenterology and hepatology. Generally, three main types of instruments are used for HRQOL measurement, namely global, generic, and disease-specific. According to literature reports, quality of life may be reduced in chronic liver diseases of various etiologies⁽⁶⁾. HRQoL has gained prominence as a tool to assess the impact of chronic diseases and their treatments on the perception of health and patient well-being⁽⁷⁾. For this purpose, Short Form 36 (SF-36), a generic instrument, and Chronic Liver Disease Questionnaire (CLDQ), which is specifically for HRQoL analysis in patients with chronic liver disease, have been used⁽⁸⁾. Studies have shown that untreated patients with chronic hepatitis C and those undergoing antiviral therapy with pegylated interferon (PEG-IFN) and ribavirin present significantly diminished quality-of-life indices⁽⁹⁾. HCV can be transmitted through intravenous drug use (IVDU), blood-to-blood contact, birth to an infected mother, blood products, organ transplantation, use of unsterilized injection needles, use of unsterilized instruments for the nose and ear piercing or tattoos, and these reasons are

the major sources of transmission of HCV in Pakistan⁽¹⁾. Treatment with antiviral medication is recommended in all people with proven chronic hepatitis C who are not at high risk of dying from other causes. People with the highest complication risk should be treated first, with the risk of complications based on the degree of liver scarring. The initial recommended treatment depends on the type of hepatitis C virus with which a person is infected⁽¹⁰⁾. With recent advances, many direct antiviral agents (DAA) developed and led to a more promising future for HCV-infected patients. Excellent advantages were related to their high potency, pan-genotypic coverage, and intermediate to high barrier to resistance⁽¹¹⁾. They paved the way for the possible application of oral interferon-free regimens. In addition, these regimens can be taken once daily and may result in global HCV eradication in the near future⁽¹²⁾. The responses to treatment are measured by the sustained viral response (SVR), defined as the absence of detectable RNA of the hepatitis C virus in blood serum for at least 24 weeks after discontinuing the treatment, and rapid virological response (RVR) defined as undetectable levels achieved within four weeks of treatment. Successful treatment decreases the future risk of hepatocellular carcinoma by 75%⁽¹³⁾. Prior to 2012, sustained response occurs in about 40–50% of people with HCV genotype 1 given 48 weeks of treatment. A sustained response is seen in 70–80% of people with HCV genotypes 2 and 3 within 24 weeks of treatment. A sustained response occurs in about 65% of those with genotype 4 after 48 weeks of treatment. The evidence for treatment in genotype 6 disease is sparse and what evidence there is supports 48 weeks of treatment at the same doses used for genotype 1 disease⁽¹⁴⁾. This work aims to improve health-related quality of life among HCV patients.

Patients and Methods

Over a period of 12 weeks, this cross-sectional study was conducted on 80 patients (60% males and 40 % females) who received direct-acting antiviral agents at the Center of Treatment of Viral Hepatitis in Ismailia Fever Hospital. It included All chronic hepatitis c virus patients who submitted to treatment with direct-acting antiviral drugs were included in the study after we had their acceptance. While patients with any other comorbid (physical or mental) disease or who refused to participate in the study were excluded. Each studied patient was subjected to detailed history taking (Age, gender, marital status, educational level, current employment, smoking, and alcohol consumption). To assess HRQoL, all study participants responded to the Chronic Liver Diseases Questionnaire (CLDQ). CLDQ is specific to assessing HRQoL in patients with chronic liver disease. The original CLDQ is a self-administered questionnaire. It consists of 29 items divided into six domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional functions, and worry. The scores calculated for each domain ranged from 1 to 7. Higher scores indicated a minimum frequency of symptoms and hence better HRQL. A total score is calculated based on the average of all 29 items⁽¹⁵⁾. Patients were asked about socio-demographic characteristics such as age, gender, marital status, education, household income, and current and prior use of drugs such as alcohol, and cigarette smoking. Blood transfusions and co-morbidities such as diabetes mellitus, hypertension, thyroid diseases, and cancer were collected⁽¹⁶⁾. Translation of CLDQ: The original CLDQ was translated into easy Arabic words for patients regarding the understandability and relevance of items.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, IL). Non-parametric variables were expressed as median and those with normal distribution as mean \pm standard deviation (SD). Descriptive statistics of all the relevant variables for the two groups were calculated. For data analysis, HRQOL indexes were compared among double therapy groups. An Independent t-test was used to compare the difference in means at each moment of therapy. A multivariate linear regression model was used to identify factors independently associated with HRQOL. Regression analysis of the variables in the correlation analysis that had $p < 0.15$ was included. For comparison, the level of significance was $P < 0.05$.

Results

This was a cross-sectional study conducted on 80 patients who received direct-acting antiviral agents with the following result. Table 1 shows that the mean age among studied patients was 52.25 years and males' predominance, according to the marital status showed that 65% were married, 45% of patients had Elementary school 70% of studied patients were employed. Table 2 shows that the mean duration of treatment among studied patients was 12 weeks and that of disease was 110.2 months. Table 3 shows that 50% of patients had no habits on the other hand 45% were smokers and 5% were alcoholics, 75% had no history of blood transfusion. Table 4 shows that 80% of patients with abdominal symptoms had low scores but as regards fatigue 50% had a low score, for systemic symptoms 50% had a low score, for activity 70% had a moderate score, for emotional functions 70% had the moderate score, worry 70% had moderate score. Table 5 shows

that as regards CLDQ item score most of the patients 90.0% of patients with bloating had a low score, 75.0% of patients with pain had a low score and 65.0% of patients

feeling Discomfort had a low score. As regards being Tired 65% had a low score, sleepy during the day 90% had a low score, decreased strength 90% had a low score,

Table 1: Distribution of the studied cases according to demographic data (n= 80)		
Age (years)		
<50	32	40.0
≥50	48	60.0
Min. – Max.	34.0 – 67.0	
Mean ± SD.	52.25 ± 9.26	
Median	54.0	
Sex		
Male	48	60.0
Female	32	40.0
Marital status		
Married	52	65.0
Divorced	16	20.0
Widowed	12	15.0
Education		
High school	32	40.0
Elementary school and below	36	45.0
College and above	12	15.0
Occupation		
Unemployed	24	30.0
Employed	56	70.0

Data are expressed as No (%)

Table 2: Distribution of the studied cases according duration of treatment and disease (n= 80).			
	No.	%	p
Duration of treatment (weeks)			<0.001*
<12	62	77.5	
≥12	18	22.5	
Min. – Max.	12.0 – 24.0		
Mean ± SD.	14.7 ± 5.04		
Median	12.0		
Duration of disease (months)			<0.001*
<100	40	50.0	
≥100	40	50.0	
Min. – Max.	5.0 – 211.0		
Mean ± SD.	110.20 ± 67.70		
Median	109.0		

P= significant at < 0.05.

drowsy, and decreased level of energy 70% a had low score regarding Bodily pain 75% a had low score, Shortness of breathing daily

65% a had low score, Muscle cramps 80% had a low score, dry mouth 70% had a low score, itching 70% had a low score, 5% had a

moderate score. Regarding Not being able to eat as they would like 65% had a low score, Trouble with carrying heavy objects 75% had a low score, and Limitations of diet 75% had a low score. Patients with the following symptoms had a low score; Anxiety (60%), Unhappiness (65%), Irritability (80%), Difficulty sleeping (75%), Mood swings (80%), inability to fall asleep (75%), depress-

sion (50%) and problems concentrating (5%). Regarding Impact on family, 30% had a low score, Symptoms developing into major problems 45% had a low score, Conditions getting worse, and never feeling any better 65% and 60% had a low score respectively. Availability of a liver 60% had a low score, and 30% had a moderate score.

Table 3: Distribution of the studied cases according to different parameters (n= 80).		
	No.	%
Special habit		
No	40	50.0
Smoking	36	45.0
Alcoholic	4	5.0
History of blood transfusion		
No	60	75.0
Yes	20	25.0

Data are expressed as percentages and frequency.

Table 4: Distribution of the studied cases according to CLDQ domains (n= 80)								
CLDQ item	Low (1-3)		Moderate (>3-5)		High (>5)		Mean \pm SD.	p
	No.	%	No.	%	No.	%		
Abdominal symptoms	64	80.0	16	20.0	0	0.0	2.72 \pm 0.91	<0.001*
Fatigue	40	50.0	40.0	50.0	0	0.0	3.04 \pm 0.79	1.000
Systemic symptoms	40	50.0	32	40.0	8	10.0	3.20 \pm 1.03	<0.001*
Activity	20	25.0	56	70.0	4	5.0	3.50 \pm 0.78	<0.001*
Emotional functions	12	15.0	56	70.0	12	15.0	3.81 \pm 0.84	0.002*
Worry	16	20.0	56	70.0	8	10.0	3.90 \pm 0.91	<0.001*

CLDQ; Chronic Liver Disease Questionnaire. P significant < 0.05.

Discussion

Egypt has the highest prevalence of Hepatitis C in the world. Overall, estimates of the HCV rate in the general population ranged between 10 and 20 percent. The treatment for Chronic Hepatitis C (CHC) is a combination therapy with pegylated interferon and ribavirin associated with many unpleasant side effects that are psychological in nature. People with CHC on combination therapy will go through phases of depression, anger, frustration, and despair as a result of the symptoms of

CHC and the side effects of therapy⁽¹⁷⁾. The recent approval of new anti-HCV regimens, including IFN-free regimens, not only has led to significant improvement in efficacy but also has provided patients with a more tolerable regimen with a shorter treatment duration. Furthermore, these regimens have been shown to be cost-effective and improve patients' HRQL and other PROs⁽¹⁸⁾. In the present study, we aimed to assess the quality of life among Egyptian Hepatitis C Virus patients before and after treatment with direct-acting antiviral drugs .80 patients were concluded. We

found that the mean age among studied patients was 52.25 years, males in predominance, the majority were married, elementary school was the most common education, and most studied patients were employed. The mean duration of disease

among studied patients was 110.2 months and the onset of treatment meantime was 15.40 weeks. 50% of patients had no habit on the other hand 45% were a smoker and 5% were alcoholics, and most of the patients had no history of blood transfusion.

Table 5: Distribution of the studied cases according to CLDQ domains (n= 80)

	Low (1 – 3)		Moderate (>3 – 5)		High (>5)		Mean ± SD.	P
	No.	%	No.	%	No.	%		
Abdominal scale								
Bloating	72	90.0	4	5.0	4	5.0	2.15 ± 1.24	<0.001*
Pain	60	75.0	12	15.0	8	10.0	2.70 ± 1.53	<0.001*
Discomfort	52	65.0	16	20.0	12	15.0	3.3 ± 1.8	<0.001*
Fatigue								
Tired or fatigued	52	65.0	20	25.0	8	10.0	3.65 ± 1.2	<0.001*
Sleepy during the day	72	90.0	4	5.0	4	5.0	2.75 ± 0.95	<0.001*
Decreased strength	72	90.0	0	0.0	8	10.0	2.70 ± 1.35	<0.001*
Drowsy, decreased level of energy	56	70.0	16	20.0	8	10.0	3.05 ± 1.57	<0.001*
Systemic symptoms								
Bodily pain	60	75.0	12	15.0	8	10.0	2.80 ± 1.20	<0.001*
Shortness of breathing during daily activities	52	65.0	12	15.0	16	20.0	3.50 ± 1.81	<0.001*
Muscle cramps	64	80.0	4	5.0	12	15.0	2.95 ± 1.7	<0.001*
Dry mouth	56	70.0	12	15.0	12	15.0	3.30 ± 1.5	<0.001*
Itching	56	70.0	4	5.0	20	25.0	3.45 ± 1.97	<0.001*
Activity								
Not able to eat as you would like	52	65.0	8	10.0	20	25.0	3.70 ± 1.8	<0.001*
Troubles with lifting or carrying heavy objects	60	75.0	8	10.0	12	15.0	3.3 ± 1.66	<0.001*
Limitation of diet	60	75.0	0	0.0	20	25.0	3.5 ± 1.87	<0.001*
Emotional functions								
Anxious	48	60.0	20	25.0	12	15.0	3.75 ± 1.27	<0.001*
Unhappy	52	65.0	8	10.0	20	25.0	4.1 ± 1.65	<0.001*
Irritable	64	80.0	4	5.0	12	15.0	3.0 ± 1.59	<0.001*
Difficulty sleeping	60	75.0	4	5.0	16	20.0	3.8 ± 1.44	<0.001*
Mood swings	64	80.0	0	0.0	16	20.0	3.60 ± 1.51	<0.001*
Unable to fall asleep	60	75.0	0	0.0	20	25.0	3.05 ± 1.87	<0.001*
Depressed	40	50.0	20	25.0	20	25.0	3.8 ± 1.90	0.007*
Problems concentrating	4	5.0	44	55.0	32	40.0	5.35 ± 1.2	<0.001*
Worry								
Impact on family	24	30.0	36	45.0	20	25.0	4.45 ± 1.33	0.074
Symptoms develop into major problems	36	45.0	28	35.0	16	20.0	4.05 ± 1.47	0.022*
Conditions getting worse	44	55.0	20	25.0	16	20.0	3.8 ± 1.58	<0.001*
Never feeling any better	48	60.0	16	20.0	16	20.0	3.85 ± 1.63	<0.001*
Availability of a liver	48	60.0	24	30.0	8	10.0	3.35 ± 1.54	<0.001*

- CLDQ; Chronic Liver Disease Questionnaire.

- Data are expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

In a similar study by Chang S-C et al they found that of the 108 enrolled patients, 59 (54.6%) were male. Age ranged from 27 to 77 years, with an average age of 55.2 years. Over half of the patients (57.4%) had an education level above junior high school, while 82 patients (75.9%) were married and lived with their families. Most patients (56.5%) were currently employed, though only 35.2% had a monthly income of more than NT\$30,000⁽¹⁹⁾. Youssef et al study showed that the baseline demographic and medical characteristics revealed that the mean age of the sample (n = 62) was $54.06 \pm$ [standard deviation (SD) 10.41 years]. The sample contained an almost equal number of males (48.4%) and females (51.6%). Most of the sample were married (72.6%) and employed (64.3%). There was an equal distribution between cirrhotic and non-cirrhotic participants, with disease discovery duration ranging from 3 to 216 months. Half of the participants had medical comorbidity, with diabetes (30.6%) and hypertension (24.2%) the most commonly reported comorbidities⁽²⁰⁾. In a study by Chang S-C et al the mean treatment duration at patient interviews was 11.19 weeks (SD = 7.78), while the treatment duration of 59 patients (54.6%) ranged from 1 to 8 weeks⁽¹⁹⁾. Another study by RODGER AJ et al showed that the mean length of time since diagnosis was 2 years (SD 1.1 years). The remaining 19 were unaware of their HCV serostatus when they were recruited and completed the SF-36 scale and all other aspects of the study. 33% of patients aware of having HCV had Consumed alcohol in the past 12 months and 100% Ever drank alcohol at least once per week⁽²¹⁾. Sobhonslidsuk et al asserted that old age had a negative impact on HRQL, the elderly is associated with less favorable appraisal of personal health due to their health concerns, pessimistic health appraisal, social isolation, and

unemployment. Instead of females having more health concerns and are more treatment seekers than male, the study found that the female gender yielded a negative influence on physical functioning, and they found marital status did not affect HRQ. This may be explained in Thai society by that CLD patients can get psychological support from other family members even when they are single or divorced. Law socioeconomic status also was shown to be an important factor affecting HRQL in the normal population. In general, the level of education can also help people cope with their own problems. Low-educated people are prone to important have psychological problems and false beliefs. People with lower socioeconomic status have more stress, more depression, and interfamilial relationship problems in their lives⁽²²⁾. Symptoms of HCV can include fatigue, weakness, general malaise, mild abdominal pain, chronic pain, and loss of appetite, although some patients may not experience any identifiable symptoms. Although research has demonstrated that HCV is associated with the development of advanced liver disease, cirrhosis, and HCC, and is a leading indication for liver transplantation⁽²³⁾. In relation to the domain of abdominal symptoms, the majority of the patients in the study sample felt abdominal Bloating, pain, and Discomfort most of the time during the time of data collection with low CLDQ scores, and rest had the moderate and high scores with decreased symptoms after treatment with antiviral therapy, This coincides with the available literature which shows that symptoms of hepatitis and cirrhosis may develop gradually when symptoms do occurs they can include abdominal bloating, abdominal indigestion or pain, nausea and vomiting, swelling or fluid buildup of the legs, and in the abdomen (ascites), vomiting blood, or blood in stool, weakness and weight

loss⁽²⁴⁾. In this study, the majority of decreased levels of energy, Sleepy during the day, decreased strength Drowsy, and Decreased levels of energy had low scores. Dienstag et al asserted that the client with hepatitis often experiences severe fatigue, leading to activity intolerance related to bed rest, fatigue, lack of energy, and altered respiratory function. Clinicians often prescribe rest for clients with cirrhosis, but how much rest is necessary is debated but it improved after receiving treatment⁽²⁵⁾. During periods of acute malfunction, rest reduces metabolic demands on the liver and increases circulation. Long-term planning should include counseling the client to rest frequently and avoid unnecessary fatigue⁽²⁶⁾. When patients were asked about systemic symptoms, the majority of Bodily pain, Shortness of breathing daily, Muscle cramps, Dry mouth, and Itching had a low score. This goes in agreement with Chung RT et al who stated that hepatitis leads to many other problems such as shortness of breathing related to increased intra-abdominal pressure on the diaphragm⁽²⁷⁾. Petta. S. C et al mentioned that muscle cramps are common in patients with HCV, especially once fluid retention develops. It can improve with the control of fluid overload and does not warrant specific treatment⁽²⁸⁾. Otherwise. Mayo. M. J et al supported that leg cramps are very common in patients with HCV. They are frequently due to decreased amounts of minerals in the body such as calcium, magnesium, and zinc. So, it is preferable for patients to take these kinds of mineral supplements to avoid cramps⁽²⁹⁾. In relation to activity, the majority of the study sample was not able to eat as they would like, had Trouble with lifting or carrying heavy objects and Limitations of diet had low scores. As reported by Blei patients with HCV had imbalanced nutrition related to impaired utilization and storage of nutrients, increased pressure on

the stomach and intestines, feeling full, anorexia, nausea, and loss of nutrients from vomiting⁽³⁰⁾. They also had activity intolerance related to anemia from poor nutrition⁽³¹⁾. In relation to the domain of the emotional function, the majority of the Anxious, Unhappy, Irritable, Difficulty sleeping, Mood swings, Unable to fall asleep, and depressed had a low score. While the majority of Problems concentrating had moderate scores. This coincides with Stein et al who emphasized that a patient who learns that he or she has contracted CLD or HCV may exhibit a range of emotional responses, including worry, fear, hopelessness, depression, and anger⁽³²⁾. In relation to the domain of worry, most of the Impact on the family had a high score. While the majority of Symptoms developing into major problems, Conditions get worse, never feel better, and the Availability of a liver had a low score. Sheikh et al asserted that neurologic changes occur with hepatitis. Sleep pattern reversal often occurs, with the client awake at night and sleepy during the day. Handwriting and speech show significant changes as intellectual deterioration occurs⁽³³⁾. The CLDQ scores in patients with HCV after receiving antiviral treatment showed that 80% of patients with abdominal symptoms had a low score 20% had a moderate score and no one had a high score but as regards fatigue, 50% had a low score, and a moderate score, for systemic symptoms 50% had low score 40% had a moderate score and 10% had a high score, activity 25% had a low score, 70% had moderate score 5% had a high score, emotional functions 15% had a low score and 70% had a moderate score and 15% had a high score, worry 20% had a low score, 70% had a moderate score and 10% had a high score. This shows the impact of antiviral treatment on in QOL of patients with HCV this is mentioned in other studies as the average CLDQ score of the 108

antiviral-treated patients was 5.23 in Chang et al.⁽¹⁹⁾ study, indicating a moderate reduction in the quality of life among antiviral-treated CHC patients and it is a lower score than that of chronic hepatitis patients treated with IFN- α in Tehran, Iran (5.40)⁽³⁴⁾, and much lower than norms in the USA (5.9)⁽³⁵⁾. This acknowledgment could help healthcare personnel understand a patient's HRQOL during treatment and guide nurses in providing better management of patient discomfort based on different impacting factors. The strength of the study is that, by selecting a representative sample of patients with CSU and of specialists involved in the treatment of CSU in Egypt, it provides a snapshot of the management of this condition from both perspectives, thereby highlighting current gaps in guideline-based care and unmet patient needs.

Conclusion

In conclusion, patients with chronic hepatitis C with or without cirrhosis have markedly reduced HRQOL. Patients who had a sustained response (virological or biochemical) to interferon therapy experienced significant improvements in perceived wellness and functional status. Successful interferon therapy provides meaningful improvements in HRQOL in patients with chronic hepatitis C.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Ethical approval

Prior to the study's conduct, ethical approval was obtained from the scientific research ethical committee. In addition, written informed consent was obtained from each participant. They were assured that anonymity and confidentiality would be

guaranteed and the right to withdraw from the study at any time.

Authors, contribution

All authors are equally contributed.

References

1. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infection*. 2011 Feb 1;17(2):107-15.
2. Alves GA, Baldessar MZ, Pereira GW, et al. Quality of life of patients with hepatitis C. *Revista da Sociedade Brasileira de Medicina Tropical*. 2012; 45:553-7.
3. El Khoury AC, Vietri J, Prajapati G. Health-related quality of life in patients with hepatitis C virus infection in Brazil. *Revista Panamericana de Salud Pública*. 2014 Mar;35(3):200-6.
4. Liu GG, daCosta DiBonaventura M, Yuan Y, et al. The burden of illness for patients with viral hepatitis C: evidence from a national survey in Japan. *Value in Health*. 2012 Jan 1;15(1): S65-71.
5. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *NEJM*. 2014 May 15;370(20):1889-98.
6. Svrtlih N, Pavic S, Terzic D, et al. Reduced quality of life in patients with chronic viral liver disease as assessed by SF12 questionnaire. *J Gastrointest Liver Dis*. 2008 Dec 1;17(4):405-9.
7. Patel R, Chang T, Greysen SR, et al. Social media use in chronic disease: a systematic review and novel taxonomy. *Am J Med*. 2015 Dec 1;128(12):1335-50.
8. Thiele M, Askgaard G, Timm HB, et al. Predictors of health-related quality of life in outpatients with cirrhosis: results from a prospective cohort. *Hepat Res Treat*. 2013; 2013:479639.
9. Chang SC, Yang SS, Chang CC, et al. Assessment of health-related quality of life in antiviral-treated Taiwanese chronic hepatitis C patients using SF-36 and CLDQ. *Health and quality of life outcomes*. 2014 Dec;12(1):1-8.

10. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015 Sep;62(3):932-54.
11. Gaetano JN. Benefit-risk assessment of new and emerging treatments for hepatitis C: focus on simeprevir and sofosbuvir. *Drug, healthcare, and patient safety*. 2014; 6:37.
12. Kohler JJ, Nettles JH, Amblard F, et al. Approaches to hepatitis C treatment and cure using NS5A inhibitors. *Infection and drug resistance*. 2014; 7:41.
13. Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med*. 2013 Mar 5;158(5_Part_1):329-37.
14. Fung J, Lai CL, Yuen MF. New paradigms for the treatment of chronic hepatitis B. *J Gastroenterol Hepatol*. 2008 Aug;23(8pt1):1182-92.
15. Mucci S, Citero VD, Gonzalez AM, et al. Cross-cultural adaptation of the Chronic Liver Disease Questionnaire (CLDQ) to the Brazilian population. *Cadernos de Saúde Pública*. 2010; 26:199-205.
16. Fleck M, Louzada S, Xavier M, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". *Revista de saúde pública*. 2000; 34:178-83.
17. Ibrahim EM, Madian A AE. Impact of Hepatitis C on Health-Related Quality of Life in Egypt. *J Am Sci* 2011;7(11).
18. Younossi ZM, Stepanova M, Henry L, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. *Clin Gastroenterol Hepatol*. 2014 Aug 1;12(8):1349-59.
19. Chang SC, Yang SS, Chang CC, et al. Assessment of health-related quality of life in antiviral-treated Taiwanese chronic hepatitis C patients using SF-36 and CLDQ. Health and quality of life outcomes. 2014 Dec;12(1):1-8.
20. Youssef NF, El Kassas M, Farag A, et al. Health-related quality of Life in patients with chronic hepatitis C receiving Sofosbuvir-based treatment, with and without Interferon: a prospective observational study in Egypt. *BMC Gastroenterol*. 2017 Dec;17(1):1-6.
21. Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology*. 1999 Nov;30(5):1299-301.
22. Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C, Khandavit A. Factors influencing health-related quality of life in chronic liver disease. *WJG*. 2006 Dec 12;12(48):7786.
23. Jessop AB, Cohen C, Burke MM, et al. Hepatitis support groups: meeting the information and support needs of hepatitis patients. *Gastroenterology Nursing*. 2004 Jul 1;27(4):163-9.
24. Garcia-Tsao G, Lim JK; Members of Veterans Affairs Hepatitis C Resource Center Program. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. *Am J Gastroenterol*. 2009 Jul;104(7):1802-29.
25. Dienstag JL, Isselbacher KJ. Acute viral hepatitis. *Harrison's principles of internal medicine*. 2005;16(2):1822.
26. Smeltzer S, Bare B, Hinkle J, et al. Suddarth's textbook of medical-surgical nursing. 10 th ed.) Philadelphia: USA: Lippincott Williams & Wilkins (2004); 1285. 2008;1298.
27. Cheung CK, Ngan RM. Improving older adults' functional ability through service use in a home care program in Hong Kong. *Research on Social Work Practice*. 2005 May;15(3):154-64.
28. Petta S, Cammà C, Scazzone C, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology*.

- 2010 Apr;51(4):1158-67.
29. Mayo MJ, Handem I, Saldana S, et al. Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology*. 2007 Mar;45(3):666-74.
30. Blei AT. Portal hypertension and its complications. *Curr Opin Gastroenterol* 2007 May 1;23(3):275-82.
31. Abraldes JG, Bosch J. The treatment of acute variceal bleeding. *J Clin Gastroenterol*. 2007 Nov 1;41: S312-7.
32. Stein MD, Maksad J, Clarke J. Hepatitis C disease among injection drug users: knowledge, perceived risk, and willingness to receive treatment. *Drug and alcohol dependence*. 2001 Feb 1;61(3):211-5.
33. Sheikh A.M, Fallon MB. Acute and Chronic Hepatitis. In T.E. Andreali. et al (EDs), *Cecil Essentials of Medicine* (6th ed). Philadelphia: saunders.; pp 399-407. 2004.
34. Noghabi AA, Zandi M, Mehran A, et al. The effect of education on quality of life in patients under interferon therapy. *Hepatitis monthly*. 2010;10(3):218.
35. Younossi ZM, Boparai N, McCormick M, et al. Assessment of utilities and health-related quality of life in patients with chronic liver disease. *Am J Gastroenterol*. 2001 Feb 1;96(2):579-83.